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# Health Effects Assessment for Ammonia

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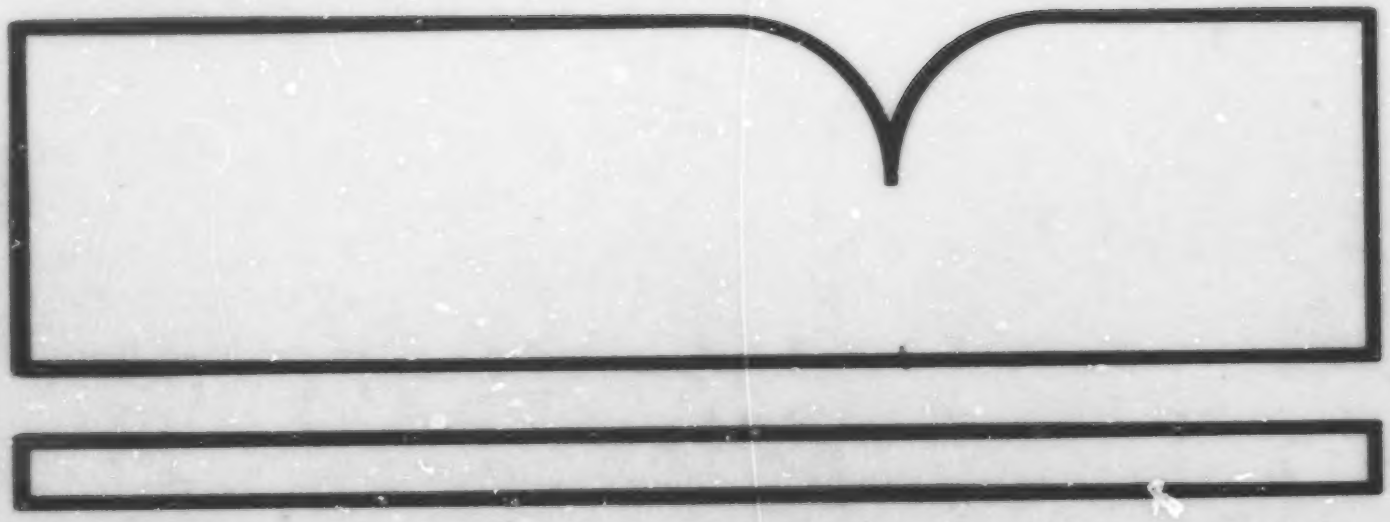

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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, $RfD_S$ or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, $q_1^*$s have been computed, if appropriate, based on oral and inhalation data if available.

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# HEALTH EFFECTS ASSESSMENT FOR AMMONIA

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## PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with ammonia. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary reflecting limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Hazard Profile for Ammonia. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1981. Ambient Water Quality Criterion for the Protection of Human Health: Ammonia. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC.

U.S. EPA. 1983. Reportable Quantity Document for Ammonia. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, $RfD_S$ (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan).

This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for $RfD_S$ estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation ($RfD_{SI}$) and oral ($RfD_{SO}$) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral ($RfD_O$) or inhalation ($RfD_I$) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity $RfD_S$ and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, $q_1^*$s have been computed, if appropriate, based on oral and inhalation data if available.

## ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Ammonia, a by-product of metabolism absorbed by the gut, normally combines with carbon dioxide to form urea. Only when this process is saturated are toxic effects of ammonia observed. Data were inadequate to develop an $RfD_{SO}$ or $RfD_{O}$. A taste threshold of 34 mg/ℓ is proposed, consistent with U.S. EPA (1981).

When inhaled, ammonia acts as an irritant on the upper respiratory tract. To protect against this effect, an $RfD_{SI}$ or $RfD_{I}$ value of 7.0 mg/day for a 70 kg human or 0.49 mg/kg/day is recommended, based on the lower-bound limit of the range for odor detection of 0.36 mg/m³ (Carson et al., 1981). A CS of 19, based on histopathological lesions in the liver, spleen and kidney of guinea pigs exposed intermittently to 119 mg/m³ (Weatherby, 1952) was chosen to represent the toxicity of ammonia.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| BUN | Blood urea nitrogen |
| bw | Body weight |
| CS | Composite score |
| $LC_{50}$ | Concentration lethal to 50% of recipients (and all other subscripted dose levels) |
| LOAEL | Lowest-observed-adverse-effect level |
| LOEL | Lowest-observed-effect level |
| MED | Minimum effective dose |
| PEL | Permissible exposure level |
| ppm | Parts per million |
| RfD | Reference dose |
| $RfD_I$ | Inhalation reference dose |
| $RfD_O$ | Oral reference dose |
| $RfD_S$ | Subchronic reference dose |
| $RfD_{SI}$ | Subchronic inhalation reference dose |
| $RfD_{SO}$ | Subchronic oral reference dose |
| RQ | Reportable Quantity |
| $RV_d$ | Dose-rating value |
| $RV_e$ | Effect-rating value |
| STEL | Short-term exposed level |
| TLV | Threshold limit value |
| TWA | Time-weighted average |

# 1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected physical and chemical properties of ammonia are presented in Table 1-1.

The atmospheric residence time of ammonia is relatively brief. Generally, combination with sulfate or washout from rainfall accounts for its rapid return to water and soil (NRC, 1979).

Ammonia is a basic compound, which commonly occurs in the environment as the positively charged ammonium ion. Ammonia/ammonium ion is an integral part of the nitrogen cycle, and its concentration in water and soil is in constant flux (NRC, 1979).

Nitrification is important in reducing the accumulation of ammonia in receiving waters. The process of nitrification proceeds in two steps each mediated by different bacterial genera:

$$NH_4^+ \xrightarrow{\text{Nitrosomonas}} NO_2^-$$

$$NO_2^- \xrightarrow{\text{Nitrobacter}} NO_3$$

This process depends upon available oxygen, temperature, pH and the microbial population (WHO, 1986). Nitrification may lead to depletion of dissolved oxygen and acidification. In addition to nitrification, physical adsorption and chemical binding to suspended solids and sediments, volatilization to the atmosphere, and assimilation by algae and macrophytes can also be important removal processes. Thus, it appears that the half-life of ammonia in water is highly variable, depending upon such factors as dissolved oxygen content, type of microbial species and microbe concentrations, pH, temperature, current speed and wind velocity as well as other factors (U.S. EPA, 1981).

TABLE 1-1

Selected Physical and Chemical Properties and Half-Lives for Ammonia

| Property | Value | Reference |
|---|---|---|
| Chemical class: | inorganic nitrogenous compound | |
| Molecular weight: | 17.03 | |
| Vapor pressure: | 10 atm at 25°C | Jones, 1973 |
| Water solubility: | $5.29 \times 10^5$ mg/ℓ at 20°C | Jones, 1973 |
| $pK_b$: | 4.77 at 20°C | HSDB, 1986 |
| Half-lives: | | |
| Air: | 16 days (less in polluted air) | NRC, 1979 |
| Soil: | days to weeks (in the unadsorbed form in warm, moist soils) | |

In soil, the ammonium ion is fairly immobile. The ammonium ion is adsorbed onto the negative adsorption sites of clay found in all soils, and the ions that are not clay-fixed undergo bacterial fixation to nitrate in soil ($t_{1/2}$ - days to weeks in warm, moist soils). In addition, relatively small quantities of ammonia are mineralized and transferred to plants. If fertilizers are applied without thorough incorporation into the soil, relatively large amounts (up to 50%) of ammonia nitrogen as gaseous $NH_3$ may volatilize rapidly under hot, dry and windy conditions (NRC, 1979).

## 2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

### 2.1. ORAL

Ammonia, which is a by-product of protein and nucleic acid metabolism, is readily absorbed by the gastrointestinal tract. Summerskill and Wolpert (1970) estimated that of the 3080 mg ammonia produced in the human gut/day, ~99% is absorbed. In healthy individuals, absorbed ammonia is mainly converted to urea in the liver so that relatively small amounts reach systemic circulation.

In a study by Conn (1972), 9 mg ammonium chloride/kg was administered orally to 20 healthy adult men and women and to 50 male patients with cirrhosis of the liver. Normal individuals showed only a transient increase in ammonia concentrations in arterial blood. Concentrations peaked (mean, 140 µg ammonia/100 mL) at 15 minutes and returned to fasting levels (mean, 105 µg ammonia/100 mL) by 30 minutes. About 50% of the subjects showed no significant rise in arterial ammonia concentrations. Individuals with cirrhosis of the liver, who had higher fasting ammonia levels (mean, 150 µg ammonia/100 mL), showed much higher blood ammonia concentrations (mean, 370 µg ammonia/100 mL) at 15 minutes, followed by a slow decrease that reflected impaired hepatic urea synthesis. In cirrhotic patients with portacaval anastomoses, ammonia blood levels were significantly higher than in patients without shunts.

Absorption of ammonia from the human colon, the major site of ammonia production, increases with increasing pH of the luminal contents (Castell and Moore, 1971). As pH increases more ammonia is in the non-ionized form and can diffuse from the gut.

There is also evidence for the active transport of ammonium ion from the gut. At a luminal pH of 5, a pH at which un-ionized ammonia would be virtually absent, Castell and Moore (1971) showed that ammonia transport by the colon, although greatly diminished, still occurred. Mossberg and Ross (1967) studied the absorption of ammonia from isolated intestinal loops of the golden hamster and concluded that the preferential site for ammonia uptake is in the ileum. In the ileum, but not in the jejunum, ammonia was found to move against a concentration gradient. Cyanide, dinitrophenol and anaerobiosis inhibited ammonia movement in the ileum, suggesting that an energy-dependent transport system was operable in the ileum but not in the jejunum. Ileal transport was not found to be dependent on pH or ammonia gradients but was observed to be dependent on carbon dioxide and carbonate concentration, providing additional evidence that ionic $NH_4^+$ was the species being actively transported (Mossberg and Ross, 1967; Mossberg, 1967).

## 2.2. INHALATION

Because it is water soluble, low concentrations of ammonia are largely absorbed in the mucous coating of the upper respiratory tract, thus protecting the lungs from exposure. Landahl and Herrmann (1950) found nasal retention of ammonia to be ~83% in humans with mean minute volumes of 6-7 ℓ, exposed to 0.05 mg/ℓ ammonia for short durations (<120 seconds). Total retention determined at ammonia concentrations between 0.04 and 0.35 mg/ℓ (40 and 350 mg/m³) was 92±2% for two male subjects tested 4 times. Retention was independent of ammonia concentration over the range tested.

Silverman et al. (1949) exposed seven male volunteers to 500 ppm (350 mg/m³) for 30 minutes. Average initial ammonia retention was not reported, but in the one example shown, initial retention was ~75%. Retention decreased progressively until equilibrium was reached in 10-27 minutes.

Retention at equilibrium averaged 23% (range 4-30%). Some irritation was observed in the nose and throat, leading the authors to suggest that at the concentration used, ammonia was primarily absorbed by the upper respiratory tract. BUN, nonprotein nitrogen, urinary urea and urinary ammonia remained normal in these subjects. This is in contrast to results reported in an abstract of a Russian study (Kustov, 1967) in which human subjects were exposed to 20 ppm (14 mg/m$^3$) for 8 hours and significant increases in BUN were observed.

Egle (1973) studied ammonia retention in anesthetized mongrel dogs (7-37/experiment). Total respiratory tract retention averaged 78% and was not related to changes in ventilation rate (5-30/minute) or ammonia concentration (214-714 ppm or 150-500 mg/m$^3$). The duration of exposure was not reported. To measure ammonia retention for the upper and lower respiratory tracts separately, Egle (1973) severed the trachea just above the bifurcation. Retention in the lower tract alone averaged 78%. Retention again averaged 78% when ammonia vapor was drawn through the nose and out the trachea and then returned. In one-way passage from the nose through the trachea, retention averaged 88%, indicating that concentrations of inhaled ammonia reaching the lungs were substantially lower than ambient concentrations.

Schaerdel et al. (1983) exposed four groups of rats (8/group) to average ammonia concentrations of 11, 23, 220 or 826 mg/m$^3$. Ammonia in the blood was measured at 0, 8, 12 and 24 hours. At the two lowest concentrations, there was no increase in blood ammonia. At the two higher doses, significant increases at the 8-hour time point were noted. After 12 and 24 hours the increases were not as marked.

## 3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

### 3.1. SUBCHRONIC TOXICITY

3.1.1. Oral. The oral toxicity of ammonia has been studied using ammonium salts as the dosing agents, and the results of these studies will be presented in this document even though many effects such as metabolic acidosis observed were the result of the anion rather than effects attributable to ammonia. Only those studies performed at doses sufficiently low to suggest thresholds are discussed here.

Lemann et al. (1966) studied the electrolyte balance of five men who received ammonium chloride. After control observations were made, the men were given total oral doses of 733 mEq ammonium chloride over a 6-day "loading period" (~93 mg/kg/day), followed by a total of 2771 mEq from days 7-18 (~177 mg/kg/day). Serum bicarbonate levels dropped initially but stabilized by day 12 of treatment and rose slightly between days 12 and 18, despite the retention of acid that occurred throughout the study. Calcium and phosphorus were lost during treatment, suggesting to the authors that the slow resorption of bone mineral was providing an additional buffering capacity. The U.S. EPA (1981) reviewed several short-term studies in humans that indicated that metabolic acidosis, impaired glucose tolerance and reduced tissue sensitivity to insulin may result from doses of ammonium chloride $\geq$100 mg/kg/day. Although frank effects were not reported, the U.S. EPA (1981) expressed concern for the potential for bone demineralization as a result of impaired acid-base balance. The U.S. EPA (1981) calculated 100 mg/kg/day of ammonium chloride to be equivalent to 31.8 mg/kg/day ammonia.

Freedman and Beeson (1961) gave 12 adult male Sprague-Dawley rats 1.6% ammonium chloride in their drinking water for up to 3 weeks and examined them for evidence of renal injury. Urinalysis and gross and histopathological examinations of the kidneys at necropsy revealed no abnormalities. Glutaminase activity per g of kidney increased with duration of exposure, indicating a physiological adaption to acidosis. An additional 10 rats were treated as above, but were then given drinking water containing 1% ammonium chloride for an additional 2.5 months. These rats also had no gross or microscopic renal abnormalities. No data on water consumption or body weights of the rats were provided: therefore, a precise daily intake cannot be calculated. Assuming the rats weighed 250 g and drank 25 mL of water/day, the rats given the 1.6% concentration or the 1% concentration in drinking water could have ingested as much as 1.6 and 1.0 g/kg bw/day, respectively, resulting in a TWA intake of ammonia of ~360 mg/kg/day. Actual intakes may have been lower because ammonium chloride is known to affect the appetite and may render the water less palatable.

In a study by Gupta et al. (1979), ammonium sulfamate was given "orally" to adult female rats and weanling male and female rats (ITRC colony-bred albino) at 100, 250 or 500 mg/kg bw/day, 6 days/week for 30, 60 or 90 days as a 10% solution in water. Twenty rats/sex/age/dose level were used. The effective dose of ammonia at each dose level is difficult to determine, since under certain conditions, sulfamate ion is hydrolyzed to bisulfate ion and ammonia, and whether this hydrolysis occurs in the rat intestine is uncertain. Assuming no hydrolysis, the ammonia doses can be estimated to be 15.0, 37.3 or 74.8 mg ammonia/kg bw/day. The effect of the anion, sulfamate and sulfate on the action of ammonium is a matter of conjecture. According

to Gupta et al. (1979) ammonium sulfamate would be expected to produce metabolic acidosis on the basis of its structure, but this result does not appear to have been verified experimentally.

The treated and control rats appeared to be healthy, and the only significant weight difference was a slight depression in the highest-dose adult females at 60 and 90 days. Food and water consumption were unaffected except in the highest-dose weanlings of both sexes, which had lower food and higher water consumption than did control weanlings. At necropsy, hematological and histological examinations were conducted. No significant differences in selected nematological values were observed. Relative organ weights of all treated groups were not significantly different from controls. Histological examination of selected major organs and tissues showed no abnormalities except slight hepatic fatty degeneration in one adult female at 90 days.

3.1.2. Inhalation. Ferguson et al. (1977) exposed six volunteers (five male and one female) to ammonia for 5 weeks. The volunteers were divided into three groups and were exposed 2-6 hours/day to respective ammonia levels of 25, 50 and 100 ppm (17, 35 and 70 mg/m$^3$). Exposure patterns varied among groups, complicating the interpretation of results. A statistically significant increase in forced expiratory volume as ammonia concentration increased was reported. This increase averaged only 4% from the low to the high dose. No differences were reported among groups for respiration, forced vital capacity, pulse or blood pressure. For the group exposed to a constant pattern to 50 ppm over 6 weeks, none of the variables varied significantly. The authors claimed that subjects became inured to eye, nose and throat irritation, but this conclusion was not clearly shown by data presented (U.S. EPA, 1981).

Effects of subchronic inhalation exposure on laboratory animals are summarized in Table 3-1. Only two of these studies (Coon et al., 1970; Broderson et al., 1976) were performed at doses low enough to define thresholds and were reported in sufficient detail to permit evaluation for risk assessment.

Coon et al. (1970) exposed rats and guinea pigs of both sexes and male rabbits, monkeys and dogs to ammonia, 8 hours/day, 5 days/week for 6 weeks or continuously for 65-114 days. Ammonia concentrations used were 155 or 770 mg/m³ for intermittent exposures and 40 or 470 mg/m³ for continuous exposure, except for rats, which were also exposed to 455, 262 or 127 mg/m³ continuously. The parameters examined were histochemical determinations, blood analyses, visible signs of toxicity and histopathological examination of heart, lung, liver, kidney and spleen from all species, and brain, spinal cord and adrenals from monkeys and dogs, as well as thyroid tissue from dogs.

The only abnormality observed in any species exposed to 155 mg/m³ intermittently was evidence of focal pneumonitis in the lung of one of the three monkeys. At the 770 mg/m³ intermittent exposures, rabbits and dogs had mild to moderate lacrimation and dyspnea during the first week. These signs disappeared during the second week and no further signs of irritation or toxicity were observed. The only other observation noted was rather consistent nonspecific inflammatory changes in the lungs of exposed rats and guinea pigs that were more extensive than in control animals.

No signs of toxicity were observed in any species exposed continuously to ammonia at 40 mg/m³ for 114 days. Rats exposed continuously to ammonia at 127 mg/m³ also showed no specific chemically-induced changes. At 262

TABLE 3-1

Effects of Subchronic Inhalation Exposure on Mammals

| Species/Strain/Sex | Number | Dose ($mg/m^3$) | Duration | Effects | Reference |
|---|---|---|---|---|---|
| Rats/Sprague-Dawley and Long-Evans/ male and female | 15/group | 770, 155 | 8 hours/day, 5 days/week, 6 weeks | At 770 $mg/m^3$, lungs showed nonspecific inflammatory changes; no histopathological changes in heart, liver, kidney or spleen; no effects at 155 $mg/m^3$. | Coon et al., 1970 |
| Guinea pigs/ Princeton-derived/ male and female | 15/group | 770, 155 | 8 hours/day, 5 days/week, 6 weeks | Same as above | Coon et al., 1970 |
| Rabbits/New Zealand White/male | 3/group | 770, 155 | 8 hours/day, 5 days/week, 6 weeks | At 770 $mg/m^3$ after first week, dyspnea and lacrimation; signs disappeared in second week; no effects at 155 $mg/m^3$ | Coon et al., 1970 |
| Dogs/beagle/male | 2/group | 770, 155 | 8 hours/day, 5 days/week, 6 weeks | Same as above | Coon et al., 1970 |
| Squirrel monkeys/ male | 3/group | 770, 155 | 8 hours/day, 5 days/week, 6 weeks | At 770 $mg/m^3$, no reported effects; at 155 $mg/m^3$ focal pneumonitis in 1/3; no other effects | Coon et al., 1970 |
| Rats/Sprague-Dawley and Long-Evans/ male and female | 15 | 470 | 90 days, continuous | 13 (86%) died; consistent lung involvement: focal or diffuse interstitial pneumonitis | Coon et al., 1970 |
| | 51 | 455 | 90 days, continuous | 50 (98%) dead by day 65; mild dyspnea and nasal irritation (no histopathological examination) | |
| | 49 | 262 | 90 days, continuous | 25% had mild nasal discharge; no gross histopathological lesions | |
| | 48 | 127 | 90 days, continuous | No deaths, no toxicity, no gross lesions of organs or tissues | |
| | 15 | 40 | 114 days, continuous | Same as above | |
| Guinea pigs/ Princeton-derived/ male and female | 15/group | 470<br>40 | 90 days, 114 days, continuous | At 470 $mg/m^3$, 4/15 (27%) died; focal or diffuse interstitial pneumonitis; no effects at 40 $mg/m^3$ | Coon et al., 1970 |



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TABLE 3-1 (cont.)

| Species/Strain/Sex | Number | Dose ($mg/m^3$) | Duration | Effects | Reference |
|---|---|---|---|---|---|
| Rabbits/New Zealand White/male | 3/group | 470<br>40 | 90 days, 114 days, continuous | At 470 $mg/m^3$, no deaths: marked eye irritation with erythema, discharge and opacity over 1/4-1/2 of the cornea; focal or diffuse interstitial pneumonitis; moderate lung congestion in 2/3; no effects at 40 $mg/m^3$ | Coon et al., 1970 |
| Dogs/beagle/male | 2/group | 470<br>40 | 90 days, 114 days, continuous | At 470 $mg/m^3$, no deaths; marked eye irritation with heavy lacrimation; nasal discharge; focal or diffuse interstitial pneumonitis; hemorrhagic lesion of lung in 1/2; no effects at 40 $mg/m^3$ | Coon et al., 1970 |
| Squirrel monkeys/ male | 3/group | 470<br>40 | 90 days, 114 days, continuous | At 470 $mg/m^3$, no deaths; focal or diffuse interstitial pneumonitis; no effects at 40 | Coon et al., 1970 |
| Rats/OFA, Pf/male | 27 exposed<br>27 control | 347±12 | 3 or 8 weeks, continuous | Upper respiratory irritation and inflammatory lesions seen at 3 but not at 8 weeks | Richard et al., 1978 |
| Rats/Sherman, Pf/ male and female | 10 exposed<br>10 control | 105±24, from bedding | 75 days, continuous | Pathological changes of anterior nasal mucosa but not trachea or lungs | Broderson et al., 1976 |
| Rats/Fischer, Pf/ male and female | 12 exposed<br>12 control | 174±6, artificial source | 35 days, continuous | Same as above | Broderson et al., 1976 |
| Guinea pigs/male | 12 exposed<br>6 control | 118±21 | 6 hours/day, 5 days/week 6, 12, 18 weeks | No changes after 6 or 12 weeks; after 18 weeks, histological exam showed congestion of spleen, liver and kidneys; no lung changes observed; hemosiderosis in spleen | Weatherby, 1952 |
| Rats | NR | 100, 30 | 25 or 60 minutes every 48 hours for 3 months | At 100 $mg/m^3$, mild leukocytosis, and lungs showed evidence of interstitial pneumonia, peribronchitis and perivasculitis | Prokop'eva and Yushkov, 1975 |

NR = Not reported



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mg/m³, ~25% of the 49 rats exposed had mild nasal discharge. Nonspecific circulatory and degenerative changes in lungs and kidneys were observed but were difficult to relate specifically to ammonia inhalation.

At 455 mg/m³, 32/51 rats died by day 25 of exposure and by day 65, when the experiment was terminated, 50 had died. All rats showed mild signs of dyspnea and nasal irritation. Histopathological examinations were not performed on these rats.

At 470 mg/m³, 13/15 rats and 4/15 guinea pigs died. Dogs and rabbits showed marked eye irritation. At necropsy, moderate lung congestion was observed in two rabbits, and one dog had a hemorrhagic lesion of a lung. In all animals examined, histopathological examination showed focal or diffuse interstitial pneumonitis. Also observed in several animals of each species were calcification of renal tubular and bronchial epithelia, proliferation of renal tubular epithelium, myocardial fibrosis and fatty changes of the liver plate cells. These changes were also observed in control animals but were less severe. Throughout these experiments (Coon et al., 1970), no pathological examinations of the upper respiratory tract were made.

In a study by Broderson et al. (1976), Sherman and Fischer pathogen-free rats in groups of 10-12 of each sex were exposed to ammonia from soiled bedding at 150±35 ppm (105 mg/m³) for 75 days or to purified ammonia at 250±8 ppm (175 mg/m³) for 35 days. Pathological changes were observed in the nasal passages of all exposed rats. The changes observed were increased thickness of the respiratory and olfactory epithelium with pyknotic nuclei in many cells along the basement membrane and hyperplasia of epithelial cells with the formation of glandular crypts. These lesions decreased in intensity posteriorly. The submucosa of the nasal passages was widened by dilation of small vessels and edema. Replacement of submucosal glands with collagen was observed and a few lymphocytes and neutrophils were present.

## 3.2. CHRONIC

3.2.1. Oral. In a study by Fazekas (1939), rabbits were treated with ammonium hydroxide by gavage at 100 mg/kg bw on alternate days and then daily for up to 17 months. This treatment resulted in enlarged adrenal glands and an increase in blood pressure to 10-30 mm Hg above baseline after several months of treatment.

Barzel and Jowsey (1969) gave male Sprague-Dawley rats (250 g, 10-12/group) 1.5% ammonium chloride in their drinking water and a regular or calcium-deficient diet for 330 days. Rats on both diets showed statistically significant decreases in bone (femur) fat-free solid and calcium content as compared with controls. Bone length and plasma calcium and phosphorus levels were unaffected. Blood pH and plasma carbon dioxide were decreased only in the regular diet group. Rats in both treated groups weighed significantly less and had smaller accumulations of body fat than did control rats receiving the same diets. Similar results were obtained in intact or ovariectomized female rats treated with 1.5% ammonium chloride in the drinking water for 300 days (Barzel, 1975). A regular diet was used in both groups of rats.

Lifetime studies with ammonium hydroxide in drinking water were conducted in two strains of mice by Toth (1972). This study did not address noncarcinogenic endpoints and is not discussed further in this section.

3.2.2. Inhalation. Pertinent data regarding the effects of chronic inhalation exposure to ammonia could not be located in the available literature.

## 3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the teratogenic and reproductive effects of ammonia by either the oral or inhalation routes of exposure could not be located in the available literature.

## 3.4. TOXICANT INTERACTIONS

Dalhamn (1963) found no synergistic effect of ammonia and carbon particles on the breathing rate of rabbit tracheal cilia. In the study a technique was used in which an air pollutant mixture could be drawn into the nostrils and out through a tracheal cannula implanted in a live rabbit breathing through another tracheal opening.

Zieve et al. (1974) found that simultaneous injection of an ammonium salt and a fatty acid into normal rats or cats produced coma at lower plasma levels of ammonia and free fatty acids than single injections of the compounds. In rats, injected sodium octanoate or inhaled methanethiol interfered with the metabolism of an injected dose of ammonium acetate, as evidenced by higher blood ammonia levels than those resulting from the ammonium dose alone. The authors suggested that the synergism of these compounds plays a role in human hepatic coma.

Broderson et al. (1976) inocculated pathogen-free Sherman and Fischer rats intranasally with Mycoplasma pulmonis and then exposed the rats to ammonia at concentrations of 25-250 ppm. A dose-related increase in the prevalence of pneumonia, but not the other respiratory lesions caused by M. pulmonis, was observed.

## 4. CARCINOGENICITY

### 4.1. HUMAN DATA

No conclusive evidence of the carcinogenic potential of ammonia in humans was found; however, evidence that suggests the possibility of ammonia playing an indirect role in inducing cancer in humans is available.

4.1.1. Oral. The higher incidence of colonic cancer in countries with populations that consume diets high in animal protein and low in fiber may provide some evidence that ammonia has an etiologic role in this cancer (Visek et al., 1978) . A major detoxification product of protein is urea. Approximately 25% of this urea is excreted into the intestinal tract where it is hydrolyzed by bacterial urease to ammonia (U.S. EPA, 1981). Burkitt (1975) noted that the incidence of polyps and cancers are highest in areas of the large bowel where ammonia concentrations are highest. Burkitt (1976) hypothesized that the role of fiber in reducing colon cancer is a result of its ability to enhance excretion of nitrogenous products. Fiber also provides an increased level of fatty acids, which decreases the pH of the colon and provide anions to trap free ammonia (Cummings, 1981).

Tannenbaum et al. (1978, 1980) and Tannenbaum and Young (1980) also suggested that amonia may be converted to nitrite in the small intestines by heterotrophic nitrification and then react to form N-nitroso carcinogens. This suggestion has been disputed by Witter et al. (1981); the role of ammonia in such a process has not been proven.

4.1.2. Inhalation. Shimkin et al. (1954) reported an isolated case of a white male who showed evidence of epidermal carcinoma of the nasal septum within 6 months after being accidentally burned by a ammonia-oil mixture. This case may represent a coincidental chain of events.

Bittersohl (1971) commented on the numerous cancer cases occurring in workers who deal with ammonia in an East German factory. Ammonia exposure levels were described and concomitant exposures to asbestos were mentioned, but no information concerning the population exposed, exposure duration or cancer rates was provided.

4.2. BIOASSAYS

4.2.1. Oral. Toth (1972) administered ammonium hydroxide in drinking water at 0.1, 0.2 or 0.3% to male and female Swiss mice for their lifetime. Inbred male and female C3H mice were provided with drinking water containing 1.0% ammonium hydroxide throughout their lifetime. Average water consumption/day was reported for each sex and dose group, but animal weights were not reported. Using an average mouse weight of 30 g, respective dose estimates are 290, 490 and 565 mg/kg bw/day for Swiss mice exposed at 0.1, 0.2 and 0.3%, and 270 mg/kg bw/day for C3H mice exposed at 1%. These estimates are likely to be low if dose-related weight reduction occurred. No carcinogenic effect was noted in this study (Toth, 1972). Ammonium hydroxide did not increase or inhibit the development of adenocarcinoma of the mammary gland in C3H females, a tumor commonly occurring in this strain.

In a study by Uzvölgi and Bojan (1980), no significant increase in lung tumors was observed in mice with a high sensitivity to lung tumors after receiving 42 mg/kg ammonia 2 times/week by gavage for 4 weeks. Uzvölgi and Bojan (1985) also found that mice treated repeatedly with diethyl pyrocarbonate and ammonia by gavage developed tumors. Diethyl pyrocarbonate alone did not cause lung tumors.

4.2.2. Inhalation. Pertinent data regarding the carcinogenic potential of ammonia following inhalation exposure could not be located in the available literature.

## 4.3. OTHER RELEVANT DATA

Litton Bionetics, Inc. (1975) reported that ammonium sulfate was not mutagenic in the Salmonella and Saccharomyces systems. Other tests have suggested that ammonia may have weak mutagenic activity in lower organisms. Ammonia was found to induce back-mutations from streptomycin dependence to nondependence in Escherichia coli but only in treatment that left <2% survivors (Demerec et al., 1951). Lobashov and Smirnov (1934) and Lobashov (1937) found that ammonia showed slight mutagenic activity in Drosophila in tests where survival was <2% after treatment. Auerbach and Robson (1947) observed 0.5% sex-linked lethal mutations in Drosophila exposed to ammonia vapor in small glass containers, also suggesting a very slight mutagenic response. Rosenfeld (1952) reported that ammonia can induce clumping of chromosomes, arrest spindle formation and result in polyploidy in chick fibroblasts in vitro.

## 4.4. WEIGHT OF EVIDENCE

No conclusive evidence was found to show that ammonia is carcinogenic in humans or experimental animals. Mutagenicity assays indicate that ammonia may have slight mutagenic activity in lower organisms. Ammonia has not been tested for mutagenic potential in mammals.

Because of the lack of evidence concerning the carcinogenic potential of ammonia, ammonia can be placed in IARC Group 3, inadequate evidence of carcinogenicity. According to the EPA classification system (U.S. EPA, 1986b), ammonia is a Group D chemical, meaning that there is inadequate animal evidence of carcinogenicity.

## 5. REGULATORY STANDARDS AND CRITERIA

The ambient water quality criterion for ammonia ($NH_3$ and $NH_4^+$) for the protection of human health is 35 mg/ℓ when expressed as $NH_3$, or 28.8 mg/ℓ as ammonia-nitrogen (U.S. EPA, 1981). Because ammonia in ambient water is a greater threat to aquatic life than to human health, a maximum value for un-ionized ammonia of 0.02 mg/ℓ as $NH_3$ has been recommended (U.S. EPA, 1976; NAS, 1973). Ecological Analysts, Inc. (1981) reported that state quality standards or criteria for freshwaters vary from 0.016-0.15 mg/ℓ for un-ionized ammonia-nitrogen and from 0.02-13 mg/ℓ for total ammonia nitrogen. Criteria for several states are based on an application factor of 0.01 or 0.1 times a 96-hour $LC_{50}$ for a resident aquatic species. State standards or criteria for estuarine or oceanic waters vary from 0.001-0.6 mg/ℓ as total ammonia-nitrogen.

NAS (1973) has recommended a standard of 0.5 mg/ℓ total ammonia-nitrogen for public water supplies. This level is based on the reduction of disinfection efficiency resulting from the reaction of ammonia with chlorine and the tendency of ammonia to be indicative of recent sewage pollution.

The U.S. FDA regulates the use of ammonium compounds in foods. Specific ammonium compounds generally recognized as safe (GRAS) by the FDA include ammonium bicarbonate, ammonium carbonate, monobasic ammonium phosphate, ammonium chloride, ammonium hydroxide and dibasic ammonium phosphate. These compounds are specified as allowed in baked goods at levels not to exceed good manufacturing practice (CFR, 1986).

The ACGIH (1948) reported the maximum acceptable concentration for ammonia to be 100 ppm (70 mg/m³), which later became a TLV. The TLV was reduced to 50 ppm (35 mg/m³) to protect against respiratory irritation (ACGIH, 1963). The ACGIH (1971) recommended a TWA of 25 ppm (17.5 mg/m³) as the TLV, which was then adopted by ACGIH (1973) as the "maximum acceptable concentration without severe complaints)" and is now the present TLV (ACGIH, 1986). The ACGIH (1986) adopted 35 ppm as a STEL; the OSHA (1985) PEL is also 35 ppm (50 mg/m³).

## 6. RISK ASSESSMENT

### 6.1. SUBCHRONIC REFERENCE DOSE ($RfD_S$)

6.1.1. Oral ($RfD_{SO}$). Several subchronic studies using animals and one with humans on the effects of ammonia salts were reviewed by the U.S. EPA (1981); the more pertinent data were reviewed in Section 3.2.1. Generally, effects occurred in humans at dosages lower than those that caused effects in animals. Gupta et al. (1979) reported reduced body weight in adult female rats treated with ammonium sulfamate for up to 90 days at 500 mg/kg/day, corresponding to 74.8 mg ammonia/kg/day. Lemann et al. (1966), however, noted disturbed acid-base balance in humans receiving ammonium chloride at ~149 mg/kg/day (ammonia equivalent of ~47.4 mg/kg/day). The U.S. EPA (1980a) reviewed shorter-term studies in humans in which ammonium chloride at 100 mg/kg/day, equivalent to 31.8 mg/kg/day ammonia, was associated with disturbed acid-base balance, glucose tolerance and tissue sensitivity to insulin. Animal models may, therefore, be an inappropriate model for the toxicity of ammonia to humans. This issue is further confused by the fact that the toxicity of ammonia has not been tested; oral studies used various ammonium salts, and the contribution of the anion to the toxicity of the compound is difficult to determine.

The WHO (1986) has suggested a taste threshold of 35 mg/ℓ, which is felt to be protective for health endpoints.

6.1.2. Inhalation ($RfD_{SI}$). The pharmacokinetics of inhalation exposure to ammonia differs from that oral of exposure. Ammonia is absorbed by the mucous of the upper respiratory tract, with very little reaching the lungs (see Section 2.2.). Because ammonia concentrates in the upper respiratory tract, the first signs of toxicity are observed at this site. Unfortunately, the inhalation studies of Coon et al. (1970) and Weatherby (1952)

did not examine the upper respiratory tract for signs of toxicity. Upper respiratory tract toxicity was observed in the studies by Richard et al. (1978) and Broderson et al. (1976), which both used pathogen-free rats. Pathological changes of the respiratory tract were observed at a lower concentration in the study by Broderson et al. (1976); therefore, that study is the best animal study available for use in inhalation risk assessment.

Broderson et al. (1976) exposed 10 male and 10 female pathogen-free Sherman rats to ammonia at an average concentration of 105 mg/m³ continuously for 75 days. The pathological changes observed were increased thickness of olfactory and respiratory epithelia of the nasal cavity, showing pyknotic nuclei and hyperplasia. These lesions decreased in intensity posteriorly. The submucosa of the nasal cavity had edema and small vessels were dilated.

The LOEL observed in rats is calculated by multiplying 105 mg/m³, the exposure concentration, by the reference rat inhalation rate 0.223 m³/day and by dividing by 0.35 kg, the reference rat weight (U.S. EPA, 1980b) to obtain 66.9 mg/kg/day as a LOEL. Applying an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for individual variability, 10 for calculating an $RfD_{SI}$ from a LOEL), a possible human $RfD_{SI}$ for ammonia of 0.07 mg/kg/day of 4.9 mg/day may be calculated for a 70 kg human. This value is slightly less than the $RfD_I$ of 7.0 mg/day calculated from the odor threshold as described in Section 6.2.2. Since the choice of the odor threshold as the basis for the $RfD_I$ reflects the inadequacies associated with the animal toxicity studies, the $RfD_I$ of 0.1 mg/kg/day or 7.0 mg/day for ammonia is adopted as the $RfD_{SI}$ for ammonia. Since this is an odor threshold it is most appropriately expressed as 0.36 mg/m³.

## 6.2. REFERENCE DOSE (RfD)

6.2.1. Oral ($RfD_0$). Three chronic oral animal studies with ammonium salts were available. In one, rabbits treated by gavage with ammonium hydroxide at ~100 mg/kg/day (~48.6 mg ammonia/kg/day) by gavage for up to 17 months had enlarged adrenal glands and elevated blood pressure (Fazekas, 1939). In the other two experiments (Barzel and Jowsey, 1969; Barzel, 1975) rats of both sexes consuming ammonium chloride at 1.5% of their drinking water (estimated to be 477 mg ammonia/kg/day) for 300-330 days had decreased bone content of fat-free solid and decreased bone content of calcium. These studies fail to define thresholds for toxicity to ammonia below that (31.8 mg/kg/day) associated with disturbed acid-base balance, glucose tolerance and tissue response to insulin in humans in very short-term studies.

Ammonia is an endogenous molecule produced in the catabolism of proteins and nucleic acid and used in the synthesis of these compounds. In humans, excess ammonia is combined with carbon dioxide by the urea cycle.

Because ammonia is endogenous a toxicity-based criterion should be derived from an estimate of the amount of excess ammonia that can be tolerated without saturating homeostatic control mechanisms. Unfortunately, studies using oral exposure to address this issue are not available. The following discussion will attempt to define a clearly undesirable level of oral exposure to ammonia, as well as levels that are clearly tolerable.

The normal human absorbs ~4 g of ammonia/day, primarily from urea and protein catabolism in the gut (Summerskill and Wolpert, 1970). Using an average body weight of 70 kg, 50-60 mg/kg is a reasonable estimate of daily ammonia uptake.

The amount of excess ammonia that can be safely ingested is difficult to define. Most studies have used ammonium chloride as the dosing agent; effects in these studies are often the result of metabolic acidosis rather than effects of ammonia. In the study by Lemann et al. (1966), metabolic acidosis was induced in five human males after a TWA daily dose of 149 mg/kg ammonium chloride over an 18-day period. In shorter studies (1-8 days) [reviewed in U.S. EPA (1981)], metabolic acidosis as well as impaired glucose tolerance and tissue sensitivity to insulin has been induced in humans at doses of ammonium chloride as low as 100 mg/kg/day (DeFronzo and Beckles, 1979; Mahnensmith et al., 1979; Edelmann et al., 1967). In longer-term studies in experimental animals (see Section 3.1.1.), no adverse effects were reported at higher levels of ammonia intake.

In theory, an RfD can be calculated from the LOAEL in previous studies using accepted methodology (U.S. EPA, 1980b). RfDs calculated by this methodology (uncertainty factor of 100 for short-term human data and a factor of 1-10 for using a LOAEL) would range from 0.032-0.32 mg/kg/day, and have been rejected by the U.S. EPA (1981) as being unreasonably low when compared with daily absorption of 50-60 mg/kg ammonia from the gut. In addition, there are no reports of adverse effects associated with the ingestion of ammonia salts as food additives. Ammonia ingestion from food additives is estimated to average ~0.25 mg/kg/day (18 mg/day) and could reach ~20 mg/kg/day (~1400 mg/day) in some diets (FASEB, 1974). From this information, it is evident that an RfD somewhat higher than that calculated by normal procedures will be protective.

In lieu of adequate health data, the U.S. EPA (1981) used organoleptic data to help pinpoint acceptable ammonia intake. In a study by Campbell et al. (1958) using taste "difference tests of the triangle type," the taste

threshold was determined to be 34 mg/ℓ. A summary by Pfaffmann (1959) states that thresholds have been determined for ammonium chloride in water at 53.5, 207 and 482 mg/ℓ (17-153 mg/ℓ as ammonia). How much the chloride ion contributes to the detection of ammonium chloride is uncertain. Details of the studies finding these thresholds were not available; therefore, a meaningful comparison with the Campbell et al. (1958) study cannot be made. Because of the uncertainty in taste threshold determination, the U.S. EPA (1981) concluded that the palatability of water is not likely to be significantly affected by total ammonia levels $\leq$35 mg/ℓ (as $NH_3$). This is the same conclusion reached by WHO (1986).

The U.S. EPA (1981) recommended 35 mg/ℓ (28.8 mg/ℓ as ammonium nitrogen) as the ambient water quality criterion to protect human health. Since this criterion level is based upon an organoleptic level rather than upon systemic toxicity it would be inappropriate to extrapolate an $RfD_O$ value in units of mg/kg/day. However, there is consensus that the 35 mg/ℓ level is below that which would contribute to adverse health effects as an additional ammonia increment from contaminated water. The actual "acceptable" level in terms of health endpoints may be higher but cannot be accurately projected based upon available data.

In determining the RQ for ammonia, CS values were calculated (U.S. EPA, 1983). The values calculated from oral data are presented in Table 6-1. The highest CS for ammonia was from an inhalation study and will be presented in Section 6.2.2.

6.2.2. Inhalation ($RfD_I$). There were no chronic inhalation studies available for ammonia. One approach for deriving an $RfD_I$ is to divide the $RfD_{SI}$ by an additional uncertainty factor of 10. An $RfD_I$ of 0.007

TABLE 6-1

Composite Scores for the Oral Toxicity of Ammonia

| Compound | Species | Sex | Exposure/Dosage | Human MED[a] (mg/day as ammonia) | $RV_d$ | Effect | $RV_e$ | CS | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Ammonium chloride | rats | M | 15,000 ppm (1.5%) in drinking water for 330 days (1170 mg/kg/day) | 3985 | 1 | Decreased growth and fat accumulation, decreased calcium and fat-free solids in bone. Increased bone resorption | 7 | 7 | Barzel and Jowsey, 1969; U.S. EPA, 1983a |
| Ammonium hydroxide | rabbits | NR | 100 mg/kg bw/day for 17 months (100 mg/kg/day) | 1275 | 1 | Enlarged adrenal glands | 4 | 4 | Fazekas, 1939; U.S. EPA, 1983a |

[a]Human MED = animal dose (mg/kg/day) x (animal weight ÷ 70 kg)$^{1/3}$ x 70 kg x (ammonia ÷ ammonium chloride); rat weight = 0.25 kg; rabbit weight = 3.7 kg

NR = Not reported

mg/kg/day or 0.49 mg/day for a 70 kg human can be calculated. Because of the large amount of uncertainty in this value and because the value seems unreasonably low, it is not recommended as the $RfD_I$.

In a review of all the ammonia inhalation studies, Carson et al. (1981) recommended that, because of the lack of studies of the effects of ammonia at low concentrations, the odor threshold, 3.6 mg ammonia/$m^3$, should be the upper bound of the range of concern. Applying an uncertainty factor of 10, 0.36 mg ammonia/$m^3$ was recommended as the lower bound limit of the range of concern. In contrast, WHO (1986) concluded that the best estimate for an odor threshold was 35 mg/$m^3$ with sensitive individuals potentially able to detect ~3.5 mg/$m^3$. WHO (1986) did not draw any conclusions concerning limits for acceptable exposure. The concentration in air of 3.6 mg/$m^3$ is substantially below the TLV of 25 ppm (~18 mg/$m^3$) recommended by ACGIH (1986) intended to protect against ocular and respiratory irritation and may serve as the basis for an $RfD_I$. Since 0.36 mg/$m^3$ is the lower bound limit of the range of concern, it should not be necessary to apply an uncertainty factor of 10 for unusually sensitive individuals. Using a 70 kg human reference body and an inhalation rate of 20 $m^3$/day, the corresponding dosage is 0.1 mg/kg/day or 7.0 mg/day for ammonia. This value is slightly larger than 4.9 mg/day calculated as a possible $RfD_{SI}$. Since this value is based on potential irritation and odor detection following inhalation exposure, it is most appropriately expressed as the air concentration.

CSs for ammonia from inhalation studies are presented in Table 6-2, and were calculated using the method indicated. U.S. EPA (1983) calculated CSs using an older methodology. MEDs were calculated assuming that inhalation exposures result in equivalent absorbed doses in mg/kg/day among species and

TABLE 6-2

Composite Scores for the Inhalation Toxicity of Ammonia

| Species | Sex | Exposure/Dosage[a] (mg/kg/day) | Human MED[b] (mg/day) | $RV_d$ | Effect | $RV_e$ | CS | Reference |
|---|---|---|---|---|---|---|---|---|
| Rats | M,F | 455 mg/m³ continuously for 90 days (290 mg/kg/day) | 347[c] | 1.7 | Increased mortality, mild dyspnea and nasal irritation | 10 | 17 | Coon et al., 1970 |
| Guinea pigs | M | 119 mg/m³, 6 hours/day, 5 days/week for 18 weeks (10 mg/kg/day) | 13[c] | 3.8 | Congestion of liver, spleen and kidneys; early degenerative changes in adrenal glands, cloudy swelling in kidney tubules, increased splenic hemosiderin | 5 | 19 | Weatherby, 1952 |
| Rats PF | M,F | 105 mg/m³ continuously for 75 days (67 mg/kg/day) | 80[c] | 2.6 | Increased histological changes of olfactory and respiratory epithelium (increased thickness, hyperplasia and inflammation of upper respiratory tract) | 5 | 13 | Broderson et al., 1976 |
| Rats | M | 350 mg/m³ continuously for 8 weeks (223 mg/kg/day) | 267[c] | 1.9 | Nasal irritation and inflammation of upper respiratory tract | 5 | 9.5 | Richard et al., 1978 |

[a]Exposure dose calculated using reference body weights and inhalation rates: rats = 0.35 kg (0.233 m³/day) (U.S. EPA, 1980b); guinea pigs = 0.84 kg (0.4 m³/day) (U.S. EPA, 1986a)

[b]Human Med = animal dose (mg/kg/day) x (animal weight ÷ 70 kg)$^{1/3}$ x 70 kg = mg/day for a 70 kg human

[c]Divided by 10 to reflect less than chronic exposure

using an absorption efficiency of 0.5 (U.S. EPA, 1983). Because of the different methods of calculating MEDs, the CSs in this document are higher than those reported in U.S. EPA (1983). The highest CS, 19, was calculated for histopathological effects in the liver, kidney, adrenal and spleen of guinea pigs exposed intermittently to 119 mg/m³ (Weatherby, 1952).

## 6.3. CARCINOGENIC POTENCY ($q_1^*$)

Ammonia has not been shown to be carcinogenic by either the oral or inhalation routes of exposure; therefore, no $q_1^*$ values can be calculated.

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## APPENDIX

### Summary Table for Ammonia

| | Species | Experimental Exposure/Dose (mg/kg/day) | Effect | Reference Dose[a] ($RfD_S$ or RfD) | Reference |
|---|---|---|---|---|---|
| Inhalation $RfD_{SI}$/ $RfD_I$ (formerly AIS and AIC, respectively) | human | 0.36 mg/m³ continuous | Lower bound limit of the range of concern for odor detection | 0.36 mg/m³[b] 7.0 mg/day | Carson et al., 1981 |
| Maximum CS | guinea pigs | 119 mg/m³ 6 hours/day 5 days/week for 18 weeks (10 mg/kg/day) $RV_d$ = 3.8 | Histopathological effects in liver, kidneys, spleen | CS = 19 | Weatherby, 1952 |
| Oral $RfD_{SO}$/ $RfD_O$ | human | 34 mg/ℓ | Taste threshold | 34 mg/ℓ[c] | Campbell et al., 1958; U.S. EPA, 1981; WHO, 1986 |

[a] $RfD_S$ or RfD - mg/day for a 70 kg human

[b] Specifically related to organoleptic threshold and potential for respiratory tract irritation, not to systemic toxicity

[c] Specifically related to organoleptic threshold, actual AIC could be higher but data are inadequate to assess.